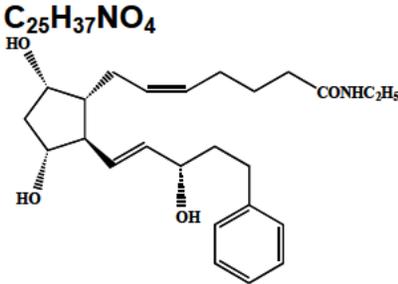


CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-369
Submission Code	Efficacy Supplement, S-010
Priority or Standard	Standard
Submit Date(s)	March 4, 2014
Received Date(s)	March 4, 2014
PDUFA Goal Date	September 4, 2014
Division / Office	DTOP/OAP
Reviewer Name(s)	Rhea A. Lloyd, MD
Review Completion Date	June 4, 2014
Established Name	Bimatoprost ophthalmic solution, 0.03%
Trade Name	Latisse
Therapeutic Class	Prostaglandin analogue
Applicant	Allergan, Inc. 2525 Dupont Drive P.O. Box 19534 Irvine, CA 92623-9534
Formulation(s)	C₂₅H₃₇NO₄  <p>The chemical structure of Bimatoprost is shown. It features a cyclopentane ring with two hydroxyl groups (HO) at the 1 and 3 positions. A propyl chain is attached to the 2-position, which is further substituted with a propyl chain ending in a primary amide group (CONHC₂H₅). A long alkyl chain (C₂₅H₃₇) is attached to the 4-position of the cyclopentane ring, containing a double bond and ending in a primary amide group (CONHC₂H₅).</p>
Dosing Regimen	Apply topically once-daily to the upper eyelid margin
Indication(s)	For the treatment of hypotrichosis of the eyelashes
Intended Population(s)	(b) (4) hypotrichosis of the eyelashes

Template Version: March 6, 2009

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(b) (4)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that the supplemental New Drug Application be approved with the labeling contained in this review.

1.2 Risk Benefit Assessment

Findings from Study 192024-040

(b) (4)

Overall findings from these studies include analysis of 'the percentage of subjects with at least a 1-grade increase from baseline on the Global Eyelash Assessment scale'.

(b) (4)

(b) (4)

The supplement supports the safety of Latisse (bimatoprost ophthalmic solution) 0.03% for the treatment of hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. The safety of bimatoprost ophthalmic solution 0.03% for the treatment of elevated intraocular pressure was demonstrated in NDA 21-275 Lumigan (bimatoprost ophthalmic solution) 0.03%. The safety of safety of bimatoprost ophthalmic solution 0.03% for the treatment of hypotrichosis of the eyelashes was demonstrated in the original submission of NDA 22-369 Latisse (bimatoprost ophthalmic solution) 0.03%. Overall, Latisse (bimatoprost ophthalmic solution) 0.03% was safe and well tolerated in Study 192024-040. Reactions most frequently associated with bimatoprost ophthalmic solution conjunctival hyperemia, conjunctivitis, eczema, erythema of the eyelid, nasopharyngitis, and sinusitis.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no Postmarket Requirements or Postmarket Commitments recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name	Bimatoprost Ophthalmic Solution, 0.03%
(Proposed) Trade Name	Latisse
Therapeutic Class	Prostaglandin analogue

Bimatoprost is an efficacious ocular hypotensive agent which was first approved for the reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension in March 2001 (NDA 21-275, Lumigan (bimatoprost ophthalmic solution, 0.03%)). The mechanisms of action by which bimatoprost reduces intraocular pressure are believed to be by increasing aqueous humor outflow through the trabecular meshwork and by enhancing uveoscleral outflow.

In the initial NDA submission, increased eyelash growth was observed as an adverse event in the clinical trials of bimatoprost 0.03% ophthalmic solution used once daily. In two active-controlled Phase 3 studies, eyelash growth was reported as an adverse event after 3 months of treatment in 17.9% and 25.6% of patients receiving bimatoprost 0.03% ophthalmic solution once daily. The proportion of subjects reporting eyelash growth increased after 6 and 12 months of treatment. In a proof-of-concept study evaluating the effect of bimatoprost 0.03% on eyelash growth, color, and thickness, bimatoprost was shown to be effective as measured by subjects' assessment of change from baseline. At the end of the 3-month treatment period, 81% (13/16) of subjects who completed the study reported their overall eyelash appearance to be "much improved," and 19% of subjects reported their overall eyelash appearance to be "improved." Lumigan (bimatoprost ophthalmic solution) 0.03% and Latisse (bimatoprost ophthalmic solution) 0.03% studied in this supplemental NDA are the same drug product.

The exact mechanism of action by which bimatoprost causes eyelash growth is unknown.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no other products currently available for this proposed indication.

2.3 Availability of Proposed Active Ingredient in the United States

Bimatoprost, the active moiety, is an efficacious ocular hypotensive agent that selectively mimics the effects of naturally occurring prostaglandins. NDA 21-275, Lumigan (bimatoprost ophthalmic solution) 0.03% was first approved in the United States in March 2001 for the reduction of intraocular pressure in patients with glaucoma or ocular hypertension.

Latisse (bimatoprost ophthalmic solution) 0.003% for the treatment of hypotrichosis of the eyelashes was approved in December 2008.

2.4 Important Safety Issues With Consideration to Related Drugs

There are four prostaglandin / prostaglandin analogue drug products which have been approved for the reduction of intraocular pressure in patients with glaucoma and ocular hypertension. As a class of drugs, the prostaglandin analogues have reported some degree of increased eyelash growth as an adverse event in their respective NDA submissions.

Latisse (bimatoprost ophthalmic solution) 0.003% for the treatment of hypotrichosis of the eyelashes was approved in December 2008.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

(b) (4)



March 27, 2013 – NDA 22-369 Submission of Final Study Report, 192024-040 in order to fulfill Postmarketing Commitment under PREA.

January 28, 2014 – Preliminary Comments for IND 109,930 Pre-NDA Meeting. (b) (4)

 The

Agency commented, "*In light of the data collected in Study 192024-040, proposed labeling may need to encompass children 5 years of age and older.*" (b) (4)

January 29, 2014 – IND 109,930 Pre-NDA Meeting. The Agency confirmed that pursuant to recommendations from the Pediatric Review Committee (PeRC), the data from Study 192024-040 is likely to be included in the Latisse Rx label. (b) (4)

February 3, 2014 – Email Communication. The Agency again confirmed that Allergan should submit an NDA supplement proposing revised pediatric labeling which should either resubmit the study report or reference the earlier submission.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There is no evidence that the studies reviewed in this supplement were not conducted in accordance with acceptable clinical ethical standards.

The results of the Clinical inspections were pending at the time of this review.

3.2 Compliance with Good Clinical Practices

The study was conducted in accordance with the International Conference of Harmonization E6 Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki and in compliance with relevant local and national regulations for informed consent and protection of subject's rights in the country of conduct.

Before initiation of the study, the original protocol, all protocol amendments, the informed consent documents and all supportive information were reviewed and approved by the appropriate ethics committees (EC) or institutional review boards (IRB) for each of the centers involved in the study. The study began after receiving written approval from each EC/IRB.

3.3 Financial Disclosures

The applicant has adequately disclosed the financial interests/arrangements with clinical investigators. None of those with significant financial interests are sponsor employees.

Allergan took the following steps to minimize potential bias of clinical study results by any of the investigators:

- The study was randomized and double-masked.
- Efficacy measures included variables derived from information recorded by the patients during the study and also variables which are objectively measured via digital image analysis.
- Investigators were not aware of the randomization block size.
- Study payments were not made contingent upon study results.

There is no evidence suggesting problems with the integrity of the submitted data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The supplement does not contain any new CMC information.

4.2 Clinical Microbiology

The supplement does not contain any Clinical Microbiology information

4.3 Preclinical Pharmacology/Toxicology

The supplement does not contain any new Preclinical information.

4.4 Clinical Pharmacology

The supplement does not contain any new Clinical Pharmacology information.

5 Sources of Clinical Data

The submitted clinical study report for Study 192024-040 was reviewed. The study was conducted in the United States and Brazil under IND 109,930 and is evaluated in this Medical Officer's review.

The supplement was submitted in eCTD format. The clinical study report was submitted March 27, 2013. The supplement was submitted March 4, 2014, with proposed labeling

and amended March 14, 2014, with the datasets. Modules 1 and 5 of all submissions were reviewed in depth.

5.2 Review Strategy

The submitted clinical study report, clinical protocol and literature reports related to study 192024-040 were reviewed. Modules 1 and 5 were reviewed in depth.

5.3 Discussion of Individual Studies/Clinical Trials

Study 192024-040: A Multicenter, Double-Masked, Randomized, Parallel-Group Study Assessing the Safety and Efficacy of Once Daily Application of Bimatoprost Solution 0.03% Compared to Vehicle When Applied to the Eyelid Margins of Pediatric Subjects

Investigators: Seven investigators participated in the study (6 in the US and 1 in Brazil)

Study Objectives

- To evaluate the safety of bimatoprost solution 0.03% once-daily bilateral application to the upper eyelid margins compared with vehicle in a pediatric population.
- To evaluate the efficacy of bimatoprost solution 0.03% once-daily bilateral application to the upper eyelid margins compared with vehicle in increasing eyelash prominence, length, thickness, and darkness in a pediatric population.

Methodology

This was a multicenter, double-masked, randomized, vehicle-controlled, parallel-group study consisting of approximately 6 or 7 scheduled visits and 1 telephone visit (screening, baseline [or a single screening/baseline combined visit], telephone visit [week 1], and months 1, 2, 3, 4 [or early exit], and 5 [post treatment follow-up]). A subject was considered to have entered the study at the time of randomization on day 1. Qualified subjects were randomly assigned to daily bilateral application to the upper eyelid margins with either bimatoprost solution 0.03% or vehicle in a 2:1 ratio.

Number of Subjects (Planned and Analyzed):

Approximately 70 subjects (approximately 30 medical-need post chemotherapy or alopecia areata pediatric subjects and approximately 40 nonmedical-need adolescents) were planned to be enrolled at approximately 15 investigational sites. At the time of randomization, eligible subjects were stratified by age group (5 to 11 versus 12 to 17 years).

Seventy-one subjects were randomized and enrolled in the study.

Diagnosis and Main Criteria for Eligibility

Diagnosis: Enrolled subjects were in 1 of the following 3 categories:

1. Pediatric subjects 5 to 17 years of age who had experienced eyelash hypotrichosis postchemotherapy and had a Global Eyelash Assessment (GEA) score of 1 (minimal), 2 (moderate), or 3 (marked) on the 4-point GEA scale
2. Pediatric subjects 5 to 17 years of age with alopecia areata who had eyelash hypotrichosis rated as a score of 1 (minimal), 2 (moderate), or 3 (marked) on the 4-point GEA scale
3. Nonmedical need adolescent subjects 15 to 17 years of age with GEA scores of 1 (minimal), 2 (moderate), or 3 (marked) on the 4-point GEA scale

Key Inclusion Criteria: Subjects who had experienced chemotherapy-induced hypotrichosis of the eyelashes (as verified by the subject and/or parent(s)/legal guardian(s)) had to be 5 to 17 years of age, inclusive, have a GEA score of 1, 2, or 3, have completed their course of intensive drug chemotherapy for cancer at least 4 weeks prior to baseline, and were postchemotherapy or on maintenance chemotherapy. For subjects who had completed their chemotherapy treatment \leq 5 years before the baseline visit, the referring oncologist must have verified that any adverse events the subject had experienced related to chemotherapy treatment, with the exception of hair loss, were resolved or were within the range acceptable to the oncologist and investigator, and anticipated the subject to be at low risk for cancer relapse for at least 6 months.

Subjects with alopecia areata-induced hypotrichosis of the eyelashes had to be 5 to 17 years of age, inclusive, and have a GEA score of 1, 2, or 3.

Nonmedical-need adolescent subjects had to be 15 to 17 years of age, inclusive, and have a GEA score of 1, 2, or 3.

All subjects had to have intraocular pressure (IOP) of \leq 20 mmHg in each eye.

Key Exclusion Criteria: Subjects were excluded if they had any uncontrolled systemic disease (other than treated cancer for postchemotherapy subjects); had received allogeneic bone marrow transplant; had gross asymmetry of right and left eyelashes whereby GEA score could not be established; had any clinically significant condition or abnormality of the lids, lashes, ocular surface, or lacrimal duct system; had scarring alopecia of the eyelid including lid tumors, herpes zoster, or other eyelid skin scarring diseases; had known or suspected trichotillomania disorder; or had any ocular pathology in either eye that might have interfered with the ability to perform required ophthalmology examinations. Subjects were excluded if they had permanent eyeliner or eyelash implants of any kind, had used over-the-counter eyelash growth products within 6 months prior to baseline, had used prescription eyelash growth products, or had treatments that might have affected hair growth within 6 months prior to baseline.

Test Product

AGN192024 0.03% sterile solution (bimatoprost ophthalmic solution 0.03%) (Allergan formulation number 9106X, batch numbers 62011, 65932, and 70013) contained 0.3 mg/mL AGN 192024, sodium phosphate dibasic (b) (4), sodium chloride, citric acid (b) (4), hydrochloric acid, sodium hydroxide, benzalkonium chloride 0.005%, and purified water.

Study treatment was applied once nightly for 4 months. One drop of study treatment was applied to a sterile, single-use-per-eye applicator and drawn along the upper eyelid margin. A second applicator was used for the contralateral eye.

Reference Therapy

AGN 192024 vehicle sterile solution (Allergan formulation number 9105X, batch numbers 13204A1, 13404A1, and 13457A1) contained sodium phosphate dibasic (b) (4), sodium chloride, citric acid (b) (4), hydrochloric acid, sodium hydroxide, benzalkonium chloride 0.005%, and purified water.

Control treatment was applied once nightly for 4 months. One drop of control treatment was applied to a sterile single-use-per-eye applicator and drawn along the upper eyelid margin. A second applicator was used for the contralateral eye.

Duration of Treatment

The study duration was 5 months. A 1-month posttreatment period followed the 4-month treatment period.

Efficacy and Safety Measurements

Efficacy: The efficacy measures were subject's overall eyelash prominence as measured by the GEA score, and the length (in millimeters [mm]), thickness/fullness (in mm²), and darkness (in intensity units) of subject's upper eyelashes as measured by digital image analysis.

Safety: The safety measures were adverse events, ophthalmic examination variables (ophthalmoscopy [dilated], biomicroscopy, IOP, iris color assessment, and best corrected visual acuity [BCVA]), physical examination, vital signs (pulse rate [beats per minute] and blood pressure [systolic/diastolic]), and urine pregnancy testing for females of childbearing potential.

Health Outcomes: The subject's satisfaction with overall eyelash prominence as measured by the validated 3-item Eyelash Satisfaction Questionnaire (ESQ-3) (for subjects aged 12 to 17 years).

Statistical Methods

Three populations were used in the analysis: safety, intent-to-treat (ITT), and per-protocol (PP). The safety population was defined as all subjects who received study medication in this study. The ITT population included all randomized subjects. The PP

population included randomized subjects with no significant protocol deviations that affected efficacy analyses. The PP population was determined prior to database lock.

Day 1 was considered as baseline. Data were summarized with descriptive statistics (sample size, mean, standard deviation, minimum/maximum, and median), frequency distributions (counts and percents), and data listings. In general, continuous variables were analyzed with descriptive statistics, with either a paired t-test performed for change from baseline and /or with 95% 2-sided confidence intervals provided, or a 2-sample t-test performed for between-group comparisons. Categorical variables were summarized with frequency distributions, with a Pearson's chi-square test, Fisher's exact test, or Cochran-Mantel-Haenszel (CMH) test performed for between-group comparisons. For ordinal categorical variable with more than 2 categories, between-group comparisons were performed using a Wilcoxon rank-sum test. For ordinal categorical variables with 2 categories, between-group comparisons were performed using a Pearson's chi-square test, Fisher's exact test, or CMH test.

The principal efficacy endpoint was the proportion of treatment responders with at least a 1-grade improvement from baseline in the GEA score at month 4. Between-group comparisons were performed using a CMH test adjusted for age group (5 to 11 vs. 12 to 17 years). A 95% 2-sided confidence interval for the difference of this efficacy variable based on CMH test was provided. For the digital image assessment variables (length, thickness/fullness, and darkness), analyses were based on the change from baseline at Month 4. Between-group comparisons were performed using a van Elteren test adjusted for age group. Missing data for the efficacy variables were imputed using last observation carried forward. All hypothesis testing was 2-sided with a significance level of 0.05.

Safety variables include study treatment exposure, adverse events, biomicroscopy, ophthalmoscopy (dilated), IOP, iris color assessment, BCVA, physical examination, physical measurement (weight and height), vital signs (pulse rate and blood pressure [systolic/diastolic]), and urine pregnancy test. All safety analyses were based on the safety population. All analyses were based on observed cases without imputation.

Table 5.3-1 - List and Description of Investigators

Site No.	Principal Investigator Name (Number) and Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
10001	Mark S. Borchert, MD The Vision Center at Children's Hospital Los Angeles 4650 Sunset Boulevard, MS/88 Los Angeles, CA 90027 USA	(b) (4)	9	1009, 1011, 1067, 1068, 1069, 1080, 1082, 1083, 1091
10003	Tanuj Nakra, MD Texas Oculoplastic Consultants & Toccare Medspa 3705 Medical Parkway, Ste 120 Austin, TX 78705 USA		0	
10004	Leslie S. Baumann, MD CPI Baumann Cosmetic and Research Institute 4500 Biscayne Boulevard Suite 100 and 105 Miami Beach, FL 33137 USA		11	1001, 1003, 1004, 1006, 1007, 1021, 1022, 1023, 1026, 1037, 1076
10012	Suzanne Bruce, MD Suzanne Bruce and Associates, PA The Center for Skin Research 1900 St. James Place, Ste 650 Houston, TX 77056 USA		14	1012, 1013, 1019, 1025, 1031, 1036, 1040, 1043, 1055, 1077, 1078, 1081, 1088, 1089
10017	Dee Anna Glaser, MD St. Louis University School of Medicine Department of Dermatology 1755 South Grand Boulevard, 1 st Floor St. Louis, MO 63104 USA		11	1008, 1024, 1039, 1045, 1061, 1062, 1063, 1073, 1074, 1085, 1090

Clinical Review
Rhea A. Lloyd, MD
NDA 22-369, S-010
Latisse (bimatoprost ophthalmic solution) 0.03%

Site No.	Principal Investigator Name (Number) and Address	Other Important Participants Name, Degree (Role)	N	Patient Numbers
10022	Steven Yoelin, MD Medical Associates, Inc. 355 Placentia, Suite 203 Newport Beach, CA 92663 USA	None	9	1032, 1046, 1049, 1050, 1051, 1052, 1065, 1075, 1084
10023	David Wirta, MD Eye Research Foundation 520 Superior Avenue, Ste 235 Newport Beach, CA 92663 USA	None	13	1027, 1028, 1029, 1030, 1033, 1034, 1038, 1041, 1042, 1053, 1054, 1060, 1064
11201	Rubens Belfort Mattos Jr., MD, PhD, MBA Unversidade Federal de Sao Paulo Escola Paulista de Medicina Hospital Sao Paulo Departamento de Oftalmologia Rua Botucatu, 820/822/824 VILA Clementino Sao Paulo – SP 04023-062 BRAZIL	(b) (4)	4	1070, 1071, 1072, 1087

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7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study 192024-040 is the only study of pediatric subjects with bimatoprost ophthalmic solution 0.03%.

Bimatoprost ophthalmic solution has been studied extensively during its clinical development program for the reduction of intraocular pressure and for the treatment of hypotrichosis in adults.

7.1.2 Categorization of Adverse Events

The protocol adequately defined an adverse event. Each investigator evaluated study participants for adverse events, volunteered and elicited, at each study visit. An Adverse Event Form was completed to document a description of the event, onset, severity, treatment required, outcome and relatedness to the use of the study medication.

The study utilized the MedDRA preferred terms for adverse event recording. The terms were sufficiently descriptive to assess adverse events expected to be experienced by the study population.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

All 71 subjects received at least one dose of study treatment and were included in the safety population.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

	Postchemotherapy Pediatric Subjects		Alopecia Areata		Non-medical Need	
	Bim 0.03% N=13	Veh N=3	Bim 0.03% N=9	Veh N=6	Bim 0.03% N=26	Veh N=14
Median study duration (days) ^a	149.0	148.0	151.0	154.5	149.5	151.0
Mean duration of treatment exposure (days)	121.2	117.0	118.1	120.2	117.3	119.8

a Duration was calculated from date of month 5 or early termination minus date of day 1 (baseline) plus 1.

b Treatment exposure was calculated from date of last dose minus date of day 1 (baseline) plus 1. If date of last dose was missing, last visit recorded for GEA was used.

Source: CSR Tables 14.6-4.1 to 14.6-5.3

Reviewer's Comment:

The median study duration and mean duration of treatment exposure were similar across the treatment groups and different etiologies.

7.2.2 Explorations for Dose Response

Studies to evaluate dose response in this indication and for the pediatric population were not performed.

7.2.3 Special Animal and/or In Vitro Testing

Special Animal and/or In Vitro Testing were not performed.

7.2.4 Routine Clinical Testing

Routine clinical testing and monitoring of study subjects were adequate to elicit adverse events.

7.2.5 Metabolic, Clearance, and Interaction Workup

Studies to evaluate metabolism, clearance and interaction were not performed due to the negligible systemic absorption of bimatoprost given by the intravitreal route of administration.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The routine clinical assessments, testing and monitoring of study subjects were adequate to elicit potential adverse events for similar drugs in the drug class.

7.3 Major Safety Results

7.3.1 Deaths

None.

7.3.2 Nonfatal Serious Adverse Events

None.

7.3.3 Dropouts and/or Discontinuations

One nonmedical need adolescent in the bimatoprost treatment group discontinued treatment due to an adverse event – exacerbation of eczema on face.

7.3.4 Significant Adverse Events

None.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

**Table 7.4.1-1 All Adverse Events with Incidence > 1 Subject in Either Treatment Group
Treatment and Posttreatment Periods Combined
(Safety Population)**

Adverse Event (Preferred Term^a)	System Organ Class	Bimatoprost 0.03% (N=48)	Vehicle (N=23)
Conjunctival hyperemia	Eye Disorders	2 (4.2%)	0 (0.0)
Conjunctivitis	Eye Disorders	2 (4.2%)	0 (0.0)
Eczema	Skin and subcutaneous tissue disorders	2 (4.2%)	0 (0.0)
Erythema of eyelid	Eye Disorders	2 (4.2%)	0 (0.0)
Nasopharyngitis	Infections and Infestations	2 (4.2%)	0 (0.0)
Sinusitis	Infections and Infestations	2 (4.2%)	0 (0.0)

Note: All adverse events, regardless of relationship to treatment, with incidence >1 subject in either treatment group, are presented. Preferred terms are sorted by descending frequency in treatment groups from left to right. Within each preferred term, a subject is counted at most once.

a MedDRA Version 15.1

Source: Table 14.3-5.1

Reviewer's Comment:

The adverse event profile is consistent with those reported in previous studies of bimatoprost ophthalmic solution.

There were no reports of iris hyperpigmentation or skin hyperpigmentation.

7.4.2 Laboratory Findings

Laboratory testing was not performed.

7.4.3 Vital Signs

No clinically meaningful changes and no statistically significant between-group differences in vital signs were observed during the study.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not performed as a part of the study.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed.

7.4.6 Immunogenicity

There have been no bimatoprost clinical studies performed and no Postmarketing data suggests immunogenic potential.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Studies to evaluate dose dependency in the occurrence of adverse events were not performed.

7.5.2 Time Dependency for Adverse Events

Studies to evaluate time dependency in the occurrence of adverse events were not performed.

7.5.3 Drug-Demographic Interactions

Study 192024-040 submitted in this supplement is the only study of the safety and efficacy of bimatoprost in pediatric subjects.

Reviewer's Comment:

The majority of enrolled subjects were nonmedical need adolescents aged 15 to 17 years. Younger subjects were enrolled in smaller numbers. No safety issues arose.

7.5.4 Drug-Disease Interactions

Study 192024-040 submitted in this supplement is the only study of the safety and efficacy of bimatoprost in pediatric subjects who are postchemotherapy and who have alopecia areata.

Reviewer's Comment:

Although no safety issues were identified, [REDACTED] (b) (4)

7.5.5 Drug-Drug Interactions

No studies of drug-drug interactions were conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There have been no bimatoprost clinical studies performed and no post-marketing data suggests tumorigenic potential.

7.6.2 Human Reproduction and Pregnancy Data

There have been no clinical studies in human reproduction or pregnancy performed. No clinical study or post-marketing data suggest an effect on human reproduction or pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth (except eyelashes) were not evaluated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence for the potential for overdose or potential for abuse with bimatoprost.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

There is no post-marketing experience with bimatoprost ophthalmic solution for this indication or route of administration in pediatric patients.

9 Appendices

9.1 Literature Review/References

The medical reviewer conducted a PubMed electronic literature search to supplement the submitted review of the relevant literature. There was no significant new information found in the published literature.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting was scheduled for this supplement.

9.3 Labeling Recommendations

Following is the applicant's current approved labeling.

Applicant proposed additions are noted by underline and deletions by within the review. Reviewer proposed additions are noted by underline and deletions by within the review.

15 Page(s) of Draft Labeling have been Withheld in Full
as b4 (CCI/TS) immediately following this page

9.4 Clinical Investigator Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number: NDA 22-369

Submission Date(s): March 4, 2014

Applicant: Allergan, Inc.

Product: Latisse (bimatoprost ophthalmic solution) 0.03%

Reviewer: Rhea A. Lloyd, MD

Date of Review: May 14, 2014

Covered Clinical Study (Name and/or Number): 192024-040

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 8 Principal Investigators; 17 Sub-Investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>None</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>3</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>None</u> Significant payments of other sorts: <u>Two</u> Proprietary interest in the product tested held by investigator: <u>None</u> Significant equity interest held by investigator in sponsor of covered study: <u>One</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3)
None

Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/> (Request explanation from applicant)
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Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed the financial interests/arrangements with clinical investigators. None of those with significant financial interests are sponsor employees.

- (b) (6) - (Significant equity interest in the applicant – stock ownership)
- (b) (6) - (Consultation fees and honoraria over \$25,000)
- (b) (6) - (Consultation fees and honoraria over \$25,000)

Allergan took the following steps to minimize potential bias of clinical study results by any of the investigators:

- *The study was randomized and double-masked.*
- *Efficacy measures included variables derived from information recorded by the patients during the study and also variables which are objectively measured via digital image analysis.*
- *Investigators were not aware of the randomization block size.*
- *Study payments were not made contingent upon study results.*

¹ See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RHEA A LLOYD
06/24/2014

WILLIAM M BOYD
06/24/2014